AMENDED SPECIFICATION

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# PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

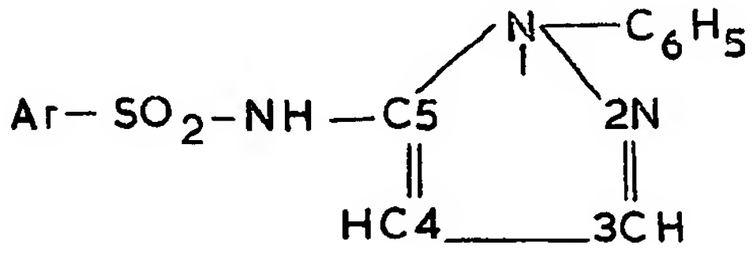
## 5-Benzene-Sulphonamido-1-Phenyl Pyrazole Derivatives

We, FARBENFABRIKEN BAYER AKTIENGESELLSCHAFT, a body corporate organised under the laws of Germany, of 22c Leverkusen-Bayerwerk, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with new and therapeutically useful-5-benzene sulphonamido-1-phenylpyrazoles and with a process for the production thereof.

It has already been established that 4-aminobenzene sulphonyl butyl urea enhances the functional capacity of the damaged liver. No therapeutic advantage can be taken of this effect because the hypoglycaemic and strong bacteriostatic properties simultaneously possessed by the 4-aminobenzene sulphonyl butyl urea result in highly undesirable and sometimes critical side effects when it is used in the treatment of hepatic disorders.

We have now found that 5-benzene sulphonamido-1-phenylpyrazoles of the general formula:




in which Ar represents a benzene ring which is substituted in the 2-position with an alkyl radical containing 1 or 2 carbon atoms or an alkoxy radical containing 1 to 4 carbon atoms and which may be substituted by an alkyl radical containing 1 or 2 carbon atoms in the 3- and/or 4-position of the pyrazole ring or which have co-condensed in the 3,4 positions of the pyrazole ring a cycloaliphatic 5-membered or 6-membered ring, have a pronounced protective effect on the liver and do not give rise to the harmful side effects of 4-aminobenzene sulphonyl butyl urea.

The new 5-benzene sulphonamido-1-phenylpyrazoles may be produced by reacting a 5-amino-1-phenylpyrazole, which may be substituted by an alkyl radical containing 1 or 2 carbon atoms in the 3- and/or 4-position or with which a cycloaliphatic 5-membered or 6 membered ring may have been co-condensed in the 3,4-position, or a salt thereof, with a benzene-sulphonyl halide, which is substituted in the 2-position of the benzene nucleus by an alkyl radical containing 1 or 2 carbon atoms or an alkoxy radical containing 1 to 4 carbon atoms in the presence of acid acceptors.

The starting 5-amino-1-phenyl-pyrazoles may be obtained in accordance with various known methods, such as by reacting phenyl hydrazines with acrylonitrile to yield N-phenyl-$N^1$-($\beta$-cyanoethyl)-hydrazines and cyclizing these compounds with sulphuric acid with simultaneous dehydration with ferric salts as described in Helv. Chim, Acta XLI (1958), page 306.

Examples of 5-amino-1-phenyl pyrazoles which may be used in accordance with the invention are 5 - amino - 1 - phenylpyrazole, 5 - amino - 1 - phenyl - 3,4 - dimethylpyrazole, 5 - amino - 1 - phenyl - 3 - methyl-4 - ethylpyrazole, 5 - amino - 1 - phenyl-3,4 - trimethylenepyrazole and 5 - amino - 1-phenyl - 3,4 - tetramethylenepyrazole.

As acid acceptors, the inorganic and organic bases, such as the trialkylamines, pyridine, potassium carbonate and sodium carbonate may be used.

The reaction may be carried out employing inert solvents or diluents, such as methylene chloride, diphenyl ether, diphenyl methane,

paraffin oil, decahydronaphthalene, tetrahydronaphthalene, methyl- and chloro-naphthalenes, or mixtures of these substances. Alternatively, the reaction may be effected in the absence of solvents.

The new 5-benzene sulphonamido-1-phenylpyrazoles according to the present invention have been found to enhance the excretory function of the damaged liver in animal experiments as demonstrated by the bromsulphalein excretion test. The compounds also bring about a marked, histologically detectable regeneration of necrotized liver parenchyma. Clinically, their oral administration, for which solutions of their alkali metal salts may be utilised, leads to significant functional improvement in acute and chronic liver disturbances. Such conditions include acute hepatitis, acute attacks of chronic hepatitis, outbreaks of necrosis in cirrhosis of the liver and hepatic coma.

The following Examples are given by way of illustration:

EXAMPLE 1.

0.1 mole 5 - amino - 1 - phenyl - 3-methyl - pyrazole are dissolved in 150 cc pyridine and then 19 g. toluene sulphonyl chloride is added while stirring and cooling with ice. After 12 hours of stirring at 20°C., excess pyridine is evaporated under vacuum and the residue digested with a 10% hydrochloric acid, causing the initially oily mass to solidify in crystalline form. Recrystallisation from aqueous alcohol gives colourless crystals of 5 - $2^1$ - methyl - benzene - sulphonamido-1 - phenyl - 3 - methyl - pyrazole which melt at 163—165°C.

Analogously, 5 - ($2^1$ - methylbenzene - sulphonamido) - 1 - phenylpyrazole of m.p. 118—119°C. from 5 - amino - 1 - phenylpyrazole and *o* - toluene - sulphonyl chloride; 5 - ($2^1$ - methylbenzene - sulphonamido) - 1-phenyl - 3,4 - dimethylpyrazole of m.p. 168—169° from 5 - amino - 1 - phenyl - 3,4-dimethyl - pyrazole (m.p. 104—107°C., prepared according to J.pr.Chem. [2] *79*, page 16) and *o* - toluene -sulphonyl chloride; 5 - ($2^1$-methylbenzene - sulphonamido) - 1 - phenyl-3 - methyl - 4 - ethylpyrazole of m.p. 133—134°C. from 5 - amino - 1 - phenyl - 3-methyl - 4 - ethylpyrazole (m.p. 76—78°C) and *o* - toluene - sulphonyl chloride; 5 - ($2^1$-methylbenzenesulphonamido) - 1 - phenyl - 3,4 - trimethylene - pyrazole of m.p. 202—204°C. from 5 - amino - 1 - phenyl - 3,4-trimethylene - pyrazole of m.p. 186—189°C. and *o* - toluene - sulphonyl chloride and 5-($2^1$ - methylbenzene - sulphonamido) - 1-phenyl - 3,4 - tetramethylene - pyrazole of m.p. 193—195°C. from 5 - amino - 1 - phenyl - 3,4 - tetramethylene - pyrazole of m.p. 145—148°C. and *o* - toluene - sulphonyl chloride.

The bis-sulphonamido compounds obtained can, in some cases, be easily converted into the monosulphonamides by briefly boiling with dilute sodium hydroxide solution.

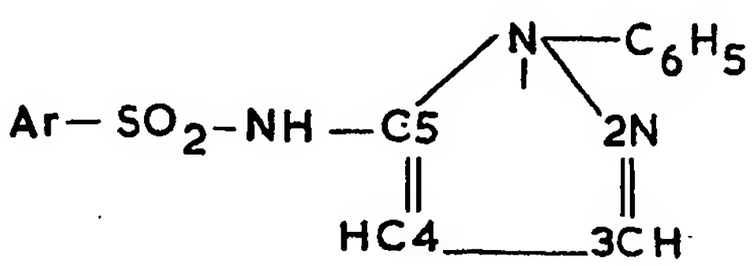
The excretory efficiency of the liver is used to demonstrate the function of the liver by excreting the dyestuff bromsulphalein. The test is carried out on rats whose liver had been damaged by application of carbon tetrachloride. The activity of the compounds is shown in the Table. The dyestuff excretion by the liver of normal rats is equal to 100 per cent, those of controls having a damaged liver—the controls get only physiological salt solution—to 0%.

| Compound | Total dose mg./100 g. of rat *per os* administered in four doses | bromsulphalein excretion in % |
|---|---|---|
| 5-($2^1$methylbenzene-sulphonamido)-1-phenyl-3,4-trimethylene-pyrazole | 4 mg. | 33% |
| | 35 mg. | 71.5% |
| | 155 mg. | 87% |
| 5-(2-methylbenzene-sulphonamido)-1-phenylpyrazole | 4 mg. | 37% |
| | 35 mg. | 51.5% |
| | 155 mg. | 76.5% |
| 5-($2^1$-methylbenzene-sulphonamido)-1-phenyl-3-methylpyrazole | 4 mg. | 74.5% |
| | 35 mg. | 75.5% |
| | 155 mg. | 86.5% |

The improvement of the liver efficiency is further proven by the determination of the activity of the enzyme fructose-1, 6-diphospho-aldolase in the serum. If the aldolase activity in the serum of animals, whose liver has been damaged and which are untreated, is equal to 100%, the use of 5-(2¹-methylbenzenesulphonamido) - 1 - phenyl - 3,4 - trimethylene-pyrazole in a total dose of 35 mg./100 g. of rat *per os* (administered in four doses) causes lowering of the enzyme activity to 59%.

WHAT WE CLAIM IS:—

1. 5 - benzene - sulphonamido - 1 - phenyl pyrazole derivatives of the general formula




in which Ar is a benzene ring, which is substituted in the 2-position with an alkyl radical containing 1 or 2 carbon atoms or an alkoxy radical containing 1 to 4 carbon atoms, and in which the 3- and/or 4-position of the pyrazole ring may be substituted with an alkyl radical containing 1 or 2 carbon atoms or in which the 3,4-positions of the pyrazole ring may be co-condensed with a 5- or 6-membered cycloaliphatic ring; and the alkali metal salts thereof.

2. 5 - (2¹ - methylbenzene - sulphonamido)-1 - phenyl - 3 - methyl pyrazole.

3. 5 - (2¹ - methylbenzene - sulphonamido)-1 - phenyl - pyrazole.

4. 5 - (2¹ - methylbenzene - sulphonamido)-1 - phenyl - 3,4 - dimethyl pyrazole.

5. 5 - (2¹ - methylbenzene - sulphonamide)-1 - phenyl - 3 - methyl - 4 - ethyl pyrazole.

6. 5 - (2¹ - methylbenzene - sulphonamido)-1 - phenyl - 3,4 - trimethylene pyrazole.

7. 5 - (2¹ - methylbenzene - sulphonamido)-1 - phenyl - 3,4 - tetramethylene pyrazole.

8. Process for the production of pyrazole derivatives of the general formula given in claim 1, wherein a 5-amino-1-phenyl pyrazole, which may be substituted by an alkyl radical containing 1 or 2 carbon atoms in the 3- and/or 4-position or with which a 5- or 6-membered ring may have been co-condensed in the 3,4-position, or a salt thereof, is reacted with a benzene-sulphonyl halide, which is substituted in the benzene nucleus in the 2-position by an alkyl radical containing 1 or 2 carbon atoms or alkoxy radical containing 1 to 4 carbon atoms, in the presence of an acid acceptor.

9. Process according to claim 8, wherein the acid acceptor is an organic or inorganic base.

10. Process according to claim 9, wherein the acid acceptor is a trialkylamine, pyridine, sodium carbonate or potassium carbonate.

11. Process according to any of claims 8—10, wherein the reaction is carried out in the presence of an inert solvent or diluent.

12. Process according to claim 11, wherein the inert solvent or diluent is methylene chloride, diphenyl ether, diphenyl methane, paraffin oil, decahydronaphthalene, tetrahydronaphthalene, methyl-naphthalene, chloronaphthalene or a mixture of two or more of these solvents or diluents.

13. Process for the production of pyrazole derivatives of the general formula given in claim 1, substantially as heerinbefore described.

14. Process for the production of pyrazole derivatives of the general formula given in claim 1, substantially as described in any of the specific Examples.

15. Pyrazole derivatives of the general formula given in claim 1, whenever prepared by the process according to any of claims 8—14.

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